## *Remarks*

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-18, 20-37 and 44-61 are pending in the application, with claims 1, 24 and 44 being the independent claims. New claims 56-61 are sought to be added. Support for new claims 56-59 may be found in claims 4 and 27. Support for new claim 60 may be found claim 44. Support for new claim 61 may be found page 6, line 18. Claims 1, 2, 4, 8, 9, 15, 22, 24, 25, 27, 32, 44, 45 and 47 have been amended. Support may be found in the claims and page 8, lines 32-33, of the specification. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

***Election/Restriction***

In the present Action at page 2, the Examiner has made final the requirement for restriction of the application on the basis that, *inter alia,* "[t]he different classification automatically establishes a burden to search." Applicants respectfully disagree. Applicants wish to remind the Examiner that MPEP § 803 provides that "[i]f the search and examination of an entire application can be made without serious burden, the

examiner must examine it on the merits, *even though it includes claims to distinct or independent inventions*." (Emphasis added.) Thus, the MPEP indicates that even distinct inventions, as reflected by different classification, must be searched and examined together so long as it can be done without serious burden. In the present situation, the claims of Group III (48-53) are dependent upon claim 1, and merely specify that the cell culture medium of claim 1 further comprises a cell. Needless to say, cell culture media are used for culturing cells thus further comprise a cell when used for their intended purpose. Since the Examiner must necessarily examine cell culture media containing cells when examining Group I, Applicants submit that there simply is no burden in examining Groups I and III at the same time. Rejoinder of Groups I and III is respectfully requested.

***Oath Declaration***

The Examiner has indicated that the oath or declaration is defective because "[N]on-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c)." (Office Action, page 3, lines 9-10).

Filed concurrently herewith is a new Declaration executed by the inventors. Applicants have accommodated the Examiner's request. Thus, it is respectfully requested that the objection to the Declaration be withdrawn.

***Claim Objections***

Claims 9, 22 and 32 were objected to because "claims 9 and 22 are missing a comma after 'pyridoxal', and claim 22 ends with 2 periods." Applicants respectfully traverse this objection.

Applicants note that pyridoxal isonicotinyl hydrazone (PIH) is a known oral iron chelator. No comma should be inserted in the name of this compound. Claim 22 has been amended to remove the extra period. Withdrawal of the objection to claims 9, 22 and 32 is respectfully requested.

***Rejections Under 35 U.S.C. § 112***

Claims 2, 4, 9, 15, 22, 25, 27 and 44-47 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention. Applicants respectfully traverse this rejection.

In particular, the Examiner states:

> A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. . . . In the present instance, **claims 4 and 27** recite the broad recitations "an acidic substance" and "a hydroxamate derivative", and the claims also recited "e.g., ferrous gluconate" and "e.g., acetohydroxamate acid", respectively, which are the narrower statements of the range/limitation.

(Office Action, page 4, lines 1-4 and 12-15; emphasis in original).

Applicants have amended claims 4 and 27 to delete reference to the narrow terms recited in the claims. New claims 56-59 directed to these narrow embodiments have been added. Therefore, this basis for the rejection has been accommodated.

The Examiner also states:

> Claims 2, 4, 15, 25, 27, 44, 45 and 47 contain improperly formulated markush groups because "or"s are improperly used. Correct markush language could begin with "is selected from the group consisting of:", which is followed by the list of elements and ends with a single "and" just before the last element in the list.

(Office Action, page 4, lines 16-19).

Applicants have amended the claims to include proper Markush language. Therefore, this basis for the rejection has been accommodated.

The Examiner also states:

> Claims 4, 27 and 47 recite "IRC011", "hydroxamate derivative", "prophyrin derivative", and/or "amino acid derivative". The metes and bound for these terms have not been set forth and their meaning is unclear.

(Office Action, page 4, last three lines).

Applicants respectfully disagree. Applicants respectfully direct the attention of the Examiner to page 23, lines 18-19, of the present application that mentions IRC011 and cites Rivkin *et al., Blood 90*:4180-4187 (1997) (cited by Applicants as document AR6). According to Rivkin *et al.*, IRC011 was purchased from Israel Resources Group (Haifa, Israel). The structure of IRC011 is shown in Fig. 1 of Rivkin *et al.* All cited publications are fully incorporated by reference. See page 39, lines 9-13, of the present application. Therefore, Applicants submit that the metes and bounds of the term "IRC011" are clear.

Applicants also respectfully direct the attention of the Examiner to page 23, lines 12-13, of the application which refers to acyl hydroxamate derivatives and cites U.S. Pat. Nos. 5,430,058, 5,506,266, and 5,756,825 (corresponding to documents AK3, AE4 and AA5, respectively). Again, these patents are fully incorporated by reference herein. These patents describe a large number of hydroxamate derivatives. Therefore, Applicants submit that the metes and bounds of the term "hydroxamate derivatives" is clear.

Applicants also respectfully direct the attention of the Examiner to U.S. Pat. Nos. 6,114,321, 6,107,480, 5,789,586, 5,744,598 and 5,552,132, attached herewith, which are directed to "porphyrin derivatives." In view of these patents, Applicants submit that the metes and bounds of this term are clear.

Applicants also respectfully direct the attention of the Examiner to page 23, lines 12-13, which refers to amino acid derivatives and cites U.S. Pat. Nos. 5,061,815, 5,278,329 and 5,430,164 (corresponding to documents AH2, AF3 and AA4, respectively). Again, these patents are fully incorporated by reference herein. Therefore, Applicants submit that the metes and bounds of this term are clear.

In view of the amendments and remarks above, Applicants request that the Examiner withdraw the rejections under 35 U.S.C. § 112, second paragraph.

***Rejections Under 35 U.S.C. § 102***

Claims 1-4, 8-12, 14-17, 22, 24-27, 31-35, 44-47 and 54 are rejected under 35 U.S.C. § 102(b) as being anticipated by Murad *et al.* (U.S. Pat. No. 5,328,913) (hereinafter "Murad"). Applicants respectfully traverse this rejection.

The Examiner states:

> Murad et al. (US 5328913) disclose the inclusion of 2-hydroxypyridine-N-oxide (2HNP) and fetal calf serum with Dulbecco's modified Eagles minimum essential medium (which includes amino acids, iron(III) and chloride, and thus inherently ferric chloride) to grow fibroblasts (column 5 lines 19-68).

(Office Action, page 5, lines 10-13).

Amended claim 1 is directed to a serum free cell culture medium. Amended claim 24 is directed to a serum free culture medium obtained according to the recited method. Mural does not teach a serum free culture medium. Therefore, Murad does not anticipate independent claims 1 and 24 and dependent claims 2-4, 8-12, 14-17, 22, 25-27, 31-35 and 54.

Claim 44 is directed to a kit for cultivation of a cell *in vitro*. Murad does not teach kits. Murad is directed to minoxidil analogs and the use thereof as antifibrotic agents. The cell culture medium described in col. 5 of Murad was used only to test the minoxidil and analogs on lysyl hydroxylase activity. Therefore, the rejection to claims 44-47 is in error.

Withdrawal of the rejection in view of Murad is respectfully requested.

Claims 1-4, 11, 12, 15-17, 22, 24-27, 34, 35, 44-47 and 54 were rejected under 35 U.S.C. § 102(b) as being anticipated by Testa *et al., Br. J. Haematol. 60:* 491-502 (1985) (hereinafter "Testa"). Applicants respectfully traverse this rejection.

The Examiner states:

> Testa et al (1985) disclose using picolinic acid with RPMI and fetal calf serum to grow human cells (e.g., Figure 2). RPMI contains chloride and fetal calf serum contains iron.

(Office Action, page 5, lines 16-18).

Testa *et al.* do not teach a serum free culture medium. Therefore, Testa *et al.* do not anticipate independent claims 1 and 24 and dependent claims 2-4, 8-12, 14-17, 22, 25-27, 31-35 and 54.

Testa *et al.* do not teach kits. Therefore, the rejection to claims 44-47 is in error.

Withdrawal of the rejection in view of Testa *et al.* is respectfully requested.

Claims 1-4, 11, 12, 15-17, 19-27, 34, 35, 44-47, 54 and 55 were rejected under 35 U.S.C. § 102(b) as being anticipated by Waymouth, in *Methods for the Preparation of Media, Supplements and Substrata for Serum-Free Animal Culture*, Vol. 2, Barnes, D.W. *et al.*, eds., Alan. R. Liss, Inc., New York, pp. 23-68 (1984) (hereinafter "Waymouth"). Applicants respectfully traverse this rejection.

The Examiner states:

> Waymouth (1984) discloses a serum-free medium containing amino acids, iron(III) and chloride (pages 49-54, and table 2) for use in growing human cells. Waymouth discusses preparations of concentrated forms.

(Office Action, page 6, lines 1-3).

Waymouth does not teach a serum free medium containing at least one transition metal binding compound or at least one transition element complex. The Examiner has not established that amino acids or chloride are transition metal binding compounds.

Withdrawal of the rejection is respectfully requested.

Claims 1-3, 11, 12, 15-26, 34, 35, 44-46 and 54 were rejected under 35 U.S.C. § 102(b) as being anticipated by Suhr-Jessen (WO 93/00423) (hereinafter "WO 93/00423"). Applicants respectfully traverse this rejection.

The Examiner states:

> Suhr-Jessen (WO 93/00423) disclose the use [of] citrate (an iron chelator) and $FeCl_3$ in a minimal medium to grow CHO and SP2/0 cells (examples 3-6).

(Office Action, page 6, lines 6-7).

Claims 1 and 24 have been amended to provide that the transition metal binding compound is not citrate. Therefore, claims 1 and 24 and dependent claims 2-4, 11, 12, 15-26, 34, 35 and 54 are not anticipated by WO 93/00423.

WO 93/00423 does not teach kits. Therefore, the rejection to claims 44-46 is in error.

Withdrawal of the rejection in view of WO 93/00423 is respectfully requested.

## *Conclusion*

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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## Version with markings to show changes made

***In the Claims:***

Claims 19 and 38-43 have been canceled.

Claims 56-61 have been added.

Claims 1, 2, 4, 8, 9, 15, 22, 24, 25, 27, 32, 44, 45 and 47 have been amended as follows:

1. (Once amended) A serum free cell culture medium comprising at least one transition metal binding compound or at least one transition element complex, said complex comprising at least one transition element or a salt or ion thereof complexed to at least one transition metal-binding compound, wherein said medium is capable of supporting the cultivation of a cell *in vitro*, with the proviso that said transition metal binding compound is not citrate.

2. (Once amended) The medium of claim 1, wherein said transition element is selected from the group consisting of scandium, titanium, vanadium, chromium, manganese, iron, cobalt, nickel, copper, zinc, yttrium, zirconium, niobium, molybdenum, technetium, rubidium, rhodium, palladium, silver, cadmium, lanthanum, hafnium, tantalum, tungsten, rhenium, osmium, iridium, platinum, gold, mercury, [and] actinium, [or] and salts [or ions] thereof.

4. (Once amended) The medium of claim 1, wherein said transition metal-binding compound is selected from the group consisting of a polyol, a hydroxypyridine

derivative,[,] 1,3,5-N,N',N''-tris(2,3-dihydroxybenzoyl)aminomethylbenzene, ethylenediamine-N,N'-tetramethylenephosphonic acid, trisuccin, an acidic saccharide [(e.g. ferrous gluconate)], a glycosaminoglycan, diethylenetriaminepentaacetic acid, nitrilotriacetic acid [mono-, bis-, or tris-substituted 2,2'-bipyridine,] mono-substituted 2,2'-bipyridine, bis-substituted 2,2'-bipyridine, tris-substituted 2,2'-bipyridine, a hydroxamate derivative [(e.g. acetohydroxamic acid)], an amino acid, deferoxamine, ferrioxamine, iron basic porphine, porphyrin and derivatives thereof, DOTA-lysine, a texaphyrin, a sapphyrin, a polyaminocarboxylic acid, an α-hydroxycarboxylic acid, a polyethylenecarbamate, picolinic acid, 4-pyridoxic acid, 3-hydroxy-2-pyridinemaltol, ethyl maltol, Ustilago ferrichrome, nicotinic acid-N-oxide and IRC011.

8. (Once amended) The medium of claim 1, wherein said transition metal-binding compound is a hydroxypyridine derivative.

9. (Once amended) The medium of claim 8, wherein said hydroxypyridine derivative is selected from the group consisting of 2-hydroxypyridine-N-oxide, 3-hydroxy-4-pyrone, 3-hydroxypypyrid-2-one, 3-hydroxypyrid-2-one, 3-hydroxypyrid-4-one, 1-hydroxypyrid-2-one, 1,2-dimethyl-3-hydroxypyrid-4-one, 1-methyl-3-hydroxypyrid-2-one, 3-hydroxy-2(1H)-pyridinone, [and] pyridoxal isonicotinyl hydrazone, nicotinic acid-N-oxide, and 2-hydroxy-nicotinic acid.

15. (Once amended) The cell culture medium of claim 1, said medium further comprising one or more ingredients selected from the group of ingredients consisting of

at least one amino acid, at least one vitamin, at least one inorganic salt, at least [or] one organic salt, at least one trace metal, at least one nucleotide, at least one buffering salt, at least one sugar, at least one lipid and at least one hormone.

22. (Once amended) The medium of claim1, wherein said medium does not contain transferrin.[.]

24. (Once amended) A cell culture medium obtained by combining a cell culture medium with at least one transition metal binding compound or at least one transition element complex, said complex comprising at least one transition element or a salt or ion thereof complexed to at least one transition metal-binding compound, wherein said medium is capable of supporting the cultivation of a cell *in vitro*, with the proviso that said transition metal binding compound is not citrate.

25. (Once amended) The medium obtained according to claim 24, wherein said transition element is selected from the group consisting of scandium, titanium, vanadium, chromium, manganese, iron, cobalt, nickel, copper, zinc, yttrium, zirconium, niobium, molybdenum, technetium, rubidium, rhodium, palladium, silver, cadmium, lanthanum, hafnium, tantalum, tungsten, rhenium, osmium, iridium, platinum, gold, mercury, [and] actinium, [or] and salts [or ions] thereof.

27. (Once amended) The medium obtained according to claim 24, wherein said metal-binding compound is selected from the group consisting of a polyol, a

hydroxypyridine derivative, 1,3,5-N,N',N''-tris(2,3-dihydroxybenzoyl)aminomethyl-benzene, ethylenediamine-N,N'-tetramethylenephosphonic acid, trisuccin, an acidic saccharide, a glycosaminoglycan, diethylenetriaminepentaacetic acid, nitrilotriacetic acid, [mono-, bis-, or tris-substituted 2,2'-bipyridine,] mono-substituted 2,2'-bipyridine, bis-substituted 2,2'-bipyridine, tris-substituted 2,2'-bipyridine, a hydroxamate derivative [(e.g. acetohydroxamic acid)], an amino acid derivative, deferoxamine, ferrioxamine, iron basic porphine, porphyrin and derivatives thereof, DOTA-lysine, a texaphyrin, a sapphyrin, a polyaminocarboxylic acid, an α-hydroxycarboxylic acid, a polyethylenecarbamate, picolinic acid, 4-pyridoxic acid, 3-hydroxy-2-pyridineethyl maltol, maltol, Ustilago ferrichrome, nicotinic acid-N-oxide, 2-hydroxy-nicotinic acid, and IRC011.

32. (Once amended) The medium obtained according to claim 31, wherein said hydroxypyridine derivative is selected from the group consisting of 2-hydroxypyridine-N-oxide, 3-hydroxy-4-pyrone, 3-hydroxypypyrid-2-one, 3-hydroxypyrid-4-one, 1-hydroxypyrid-2-one, 1,2-dimethyl-3-hydroxypyrid-4-one, 1-methyl-3-hydroxypyrid-2-one, 3-hydroxy-2(1H)-pyridinone, [and] pyridoxal isonicotinyl hydrazone, nicotinic acid-N-oxide, and 2-hydroxy-nicotinic acid.

44. (Once amended) A kit for the cultivation of a cell *in vitro*, said kit comprising at least one component selected from [a] the group consisting of one or more cell culture media or media ingredients, one or more metal binding compounds, one or more transition elements, one or more transition element complexes and one or more cells.

44. (Once amended) A kit for the cultivation of a cell *in vitro*, said kit comprising at least one component selected from [a] the group consisting of one or more cell culture media or media ingredients, [one or more metal binding compounds,] one or more transition elements, one or more transition element complexes and one or more cells, and at least one second component selected from the group consisting of one or more transition metal binding compounds and at least one transition element complex, said complex comprising at least one transition element or a salt or ion thereof complexed to at least one transition metal-binding compound.

45. (Once amended) The kit of claim 44, wherein said transition element is selected from the group consisting of scandium, titanium, vanadium, chromium, manganese, iron, cobalt, nickel, copper, zinc, yttrium, zirconium, niobium, molybdenum, technetium, rubidium, rhodium, palladium, silver, cadmium, lanthanum, hafnium, tantalum, tungsten, rhenium, osmium, iridium, platinum, gold, mercury, [and] actinium, [or] and salts [or ions] thereof.

47. (Once Amended) The kit of claim 44, wherein said metal-binding compound is selected from the group consisting of a polyol, a hydroxypyridine derivative, 1,3,5-N,N',N''-tris(2,3-dihydroxybenzoyl)aminomethylbenzene, ethylenediamine-N,N'-tetramethylenephosphonic acid, nitrilotriiacetic acid, trisuccin, an acidic saccharide, a glycosaminoglycan, diethylenetriaminepentaacetic acid, [mono-, bis-, or tris-substituted 2,2'-bipyridine,] mono-substituted 2,2'-bipyridine, bis-substituted 2,2'-bipyridine, tris-

substituted 2,2'-bipyridine, a hydroxamate derivative, an amino acid derivative, deferoxamine, ferrioxamine, iron basic porphine, porphyrin and derivatives thereof, DOTA-lysine, a texaphyrin, a sapphyrin, a polyaminocarboxylic acid, an α-hydroxycarboxylic acid, a polyethylenecarbamate, picolinic acid, 4-pyridoxic acid, 3-hydroxy-2-pyridineethyl maltol, maltol, Ustilago ferrichrome, and IRC011.